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09/980,525	03/18/2002	Robert D. Simari	07039-280001	5964

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EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

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Office Action Summary	Application No.	Applicant(s)	
	09/980,525	SIMARI, ROBERT D.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/13/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) *5-16,24 and 31-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,17-23 and 25-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11/15/01* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/11/02,8/14/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Non-Final Rejection

Claims 1-46 are pending.

The examiner has considered the international search report and international examination report.

Election/Restrictions

Applicant's election without traverse of Group I (claims 1, 2, 3, 4, 17-23, and 25-30) in Paper filed on 2/14/04 is acknowledged.

Claims 5-16, 24, 31-46 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper filed on 2/14/04.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Specification

The abstract of the disclosure is objected to because: The abstract of the disclosure does not commence on a separate sheet in accordance with 37 CFR 1.52(b)(4). A new abstract of the disclosure is required and must be presented on a separate sheet, apart from any other text. Correction is required. See MPEP § 608.01(b).

Claim Objections

Claims 17-23 and 25-30 are objected to because of the following informalities: the claims read on non-elected embodiment. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 17-23, and 25-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claimed invention is directed to a method of gene therapy comprising administering to a mammal a composition comprising a nucleic acid molecule comprising a nucleic acid

sequence comprising a nucleic acid segment encoding a brain natriuretic peptide (BNP) or a chimera thereof in a delivery vehicle. More specifically, the invention is directed to using the composition to inhibit or prevent heart failure in a mammal or to relax cardiac muscle in a mammal. The invention lies in the field of gene therapy.

Furthermore, and with respect to claims directed to any gene therapy treatment of a mammal; the state of the art exemplified by Anderson et al., *Nature*, Vol. 392, pp. 25-30, 1998, displays major consideration for any gene transfer or any gene therapy protocol involve issues that include:

1) The type of vector and amount of DNA constructs to be administered,

2) The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

3) The trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

4) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method.

In addition, all of these issues differ dramatically based on the specific vector used, the route of administration, the animal being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several

major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2). For additional reviews of the unpredictability of gene therapy art, see Kmiec, American Scientist, 1999, 87, 240-247; Juengst, BMJ, 2003, 326:1410-11; Orkin et al., December 7, 1995, "Report and Recommendation of the Panel to Assess the NIH investment in Research and Gene Therapy", issued by the National Institute of Health.

In addition, Askari et al., Seminars in Thoracic and Cardiovascular Surgery, 14:167-177, 2002, teaches the unpredictability for the gene therapy treatment of heart failure in a mammal. Therefore, at the time the application was filed, the state of the art for gene therapy was considered unpredictable.

With respect to the working examples, the specification contemplates locally (catheter-based to the heart) and systemically (intramuscular) delivering BNP in normal canines. The specification recites that catheter-based, adenoviral gene transfer of human BNP in dogs resulted in local and systemic BNP 3 days after infection. Furthermore, the specification contemplates

establishing whether local or systemic BNP delays the progression of ALVD to overt congestive heart failure (CHF) in a canine ALVD model. The ALVD model has progressive ventricular systolic dysfunction with ventricular dilatation and hypertrophy. In view of the definition of the ALVD model, the ALVD model is in the initial stage of heart failure (page 45, lines 17-21). The specification does not teach a BNP gene therapy method to inhibit or prevent heart failure in mammal or a BNP gene therapy method to relax cardiac muscle in a mammal. At the time the application was filed, the state of the art is absent for any method of BNP gene therapy. In addition, there are some major concerns for any method of gene therapy, including *in vivo* gene therapy for preventing a heart failure in a mammal that the as-filed specification fails to address and some of the major concerns are:

1) what amount of the expressed BNP protein is considered to be therapeutically effective for preventing heart failure in a mammal;

2) what defines "preventing" a heart failure in a mammal; and

3) what would one skilled in the art compare the claimed method to in order to ascertain that preventing heart failure in a mammal was obtained.

In addition, with respect to the amount of guidance provided, the applicant teaches how to locally and systemically express BNP for 3 days in a normal dog using catheter-based, adenoviral gene transfer of human BNP. However, the relevance of this data to the claimed methods is unclear at best because neither applicant nor the prior art provide a correlation or nexus between the data obtained in the *in vivo* study in a normal dog as those provide by applicant with the claimed methods. In addition, with respect to the prophetic examples, in view of the lack of guidance provided by the specification for sufficient guidance and/or factual

evidence for practicing the claimed methods and the unpredictability of gene therapy, the specification does not teach one skilled in the art how to practice the claimed invention without an undue amount of experimentation. Given the above analysis of the factors, it is concluded that the skilled artisan, at the time the application was filed, would have to conduct an excessive amount of experimentation in order to practice the claimed invention.

In addition, with respect to claims 1-4, 17-23, and 25-30, the claims encompass using a genus of administration routes in the claimed methods. Claims 1-4, 17, 18, 22, 23, 25-26, and 30 embrace using any route of administration. Claims 19, 20, 28, and 29 embrace using local administration to the heart. Claim 21 embraces using systemic administration. Claim 27 embraces administration to the skeletal muscle of a mammal. With respect to using a genus of administration routes in the claimed methods, the specification does not provide sufficient guidance and/or factual evidence for using the genus of administration routes. In view of the unpredictability in the art of record, one skilled in the art could not predict without undue experimentation what route other than local would deliver the composition to the heart. Furthermore, for the reasons set forth above, even if the composition is delivered to the heart, the as-filed specification does teach one skilled in the art what amount of the expressed BNP is considered to be therapeutically effective for any claimed methods using local administration. In addition, with respect to delivering the composition to the skeletal muscle of the mammal, the specification does not provide sufficient guidance and/or factual evidence for how BNP expression in the skeletal muscle reasonably correlates to sufficiently expressing BNP in the heart to inhibit or prevent heart failure or relax cardiac muscle in a mammal. The art of record

does not teach one skilled in the art how to express a therapeutic amount of BNP in the heart of a mammal by administering a composition encoding BNP to the skeletal muscle of the mammal.

As a result, it is not apparent how one skilled in the art determines, without undue experimentation, which of the claimed compositions generate a therapeutic effect, how is it apparent as to how one skilled in the art, without any undue experimentation, practices any gene therapy method as contemplated by the claims, particularly given the unpredictability of gene therapy as a whole and/or the doubts expressed in the art of record.

Furthermore, with respect to claims 1-4, 17-23, and 25-30, the claims encompass a composition comprising a nucleic acid molecule comprising a nucleic acid segment encoding a brain natriuretic peptide (BNP), which does not express BNP. The claims do not embrace a promoter operatively linked to the nucleic acid segment. The specification does not teach using an endogenous regulatory sequence from BNP. The specification provides sufficient guidance for one skilled in the art to make and use a nucleic acid segment, which expresses BNP comprising a promoter operatively linked to the nucleic acid segment encoding BNP. However, the specification fails to provide sufficient guidance or evidence for one skilled in the art to make and use a nucleic acid segment, which express BNP comprising a promoter that is not operatively linked to any specific nucleotide segment (e.g. BNP) in the nucleic acid molecule. The teachings in the specification are directed to using a promoter to express BNP. The as-filed specification provides guidance or evidence for how to make and use vectors comprising a promoter operatively linked to BNP to direct BNP expression, however the claims do not recite such a structural limitation. Thus, to the extent the claims fail to recite distinguishing features to

commensurate with the level of guidance presented, the composition in the claims is not considered enabled.

In addition, with respect to using a nucleic acid encoding a chimera of BNP or a BNP from a species different from the mammal in the claimed method, the claimed invention is not considered enabled. The specification defines "chimeric" as "a vector comprises DNA from at least two different species, or comprises DNA from the same species, which is linked or associated in a manner which does not occur in the "native" or "wild type of the species" (page 22, lines 24-27)." The claims embrace using a nucleic acid encoding a BNP that does not have native BNP biological activity. The applicant produces a humanized chimeric DNP, wherein the humanized DNP was cloned downstream of the entire pre-pro sequence of the BNP or the leader sequence of BNP without the prohormone sequence (Example 4). The applicant teaches the use of a vector expressing BDNP *in vitro*. The specification does not teach what amino acids of BNP are considered essential/non-essential for observing a desired biological activity of BNP *in vivo*, e.g., inhibit or prevent heart failure. The art of record teaches that the *in vivo* biological action of BNP is species-specific (Kambayashi et al., Biochemical and Biophysical Research Communications, 173, 599-605, 1990). In view of the art of record and the lack of guidance provided by the specification for using a chimeric BNP or a different species of BNP (e.g., canine BNP in a human) in the claimed methods, the relevance of this data to the claimed methods is unclear at best because neither the applicant nor the prior art provide a correlation or nexus between the results obtained *in vitro* studies as those provide by the applicant with the results which the skilled artisan would reasonably expect to see *in vivo*. Furthermore, the court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

It is well settled that patent applications are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.
In re Vaeck, 947 F.2d 48, 496 & n.23. 30 USPQ2d 1438, 1445 &n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specification provide no more than a "plan" or "invitation" for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel. 984 F.2d.1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [Footnote omitted].

On this record, it is apparent that the specification provides no more than a plan or invitation in view of the art of record teaching that the *in vivo* biological action of BNP is species-specific, for those skilled in the art to further experiment with BNP chimeras or using a species of BNP different from the mammal as intended by the as-filed specification at the time the invention was made.

In conclusion, the as-filed specification and claims coupled with the art of record, at the time the invention was made, do not provide sufficient guidance and/or evidence to reasonably enable the claimed invention. Given that gene therapy wherein any delivery vehicle is employed to correct a disease or a medical condition in any mammal was unpredictable at the time the invention was made, and given the lack of sufficient guidance as to a gene therapy effect produced by any delivery vehicle cited in the claims, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the applicant's disclosure and the unpredictability of gene therapy.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764.

The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, SPE - Art Unit 1635, can be reached at (571) 272-0760.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER